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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/588,555	06/01/2007	Allan Svendsen	10517.204-US	5093

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EXAMINER	
SWOPE, SHERIDAN	

ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/588,555	SVENDSEN ET AL.	
	Examiner	Art Unit	
	SHERIDAN SWOPE	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *47-76* is/are pending in the application.

4a) Of the above claim(s) *48-58 and 61-75* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *47,59,60 and 76* is/are rejected.

7)☒ Claim(s) *47, 59, 60, and 76* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *0209*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' filing of February 24, 2009, in response to the Action of October 28, 2008 is acknowledged. It is acknowledged that Claims 15-28, 33, and 38-46 are cancelled and Claims 47-76 are added. Claims 47-76 are pending. As stated in the Action of October 28, 2008, the elected invention is directed to an RP-II protease variant of SEQ ID NO: 2 having a H144R substitution. Claims 48-58 and 61-75 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Claims 47, 59, 60, and 76 are hereby examined.

Information Disclosure Statement

The Information Disclosure Statement filed February 24, 2009 has not been considered because the references cited have not been provided.

Claims-Objections

Claims 47, 59, 60, and 76 are objected to for reciting non-elected subject matter.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Utility

Claims 47, 59, and 60 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The variant of SEQ ID NO: 2 having a $H^{144}R$ substitution is likely to occur in nature. Therefore, the recited subject matter fails to show the "hand of man". It is suggested that the term "isolated" or "recombinant" be used.

In support of their request that the prior analogous rejection be withdrawn, Applicants argue that, since the variants have modifications, they would not occur in nature. This argument is not found to be persuasive because variants having modifications do occur in nature.

Claim Rejections - 35 USC § 112-Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 76 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the following reasons.

For Claim 76, "a variant" is improper antecedent usage and should be corrected to "the variant".

Examiner's note: Regarding the phrase "RP-II protease activity" in Claim 47, it is assumed that said activity is glutamic-acid-specific endopeptidase activity, as stated in the specification [0005].

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 47, 59, 60, and 76 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID NO: 2 having a $H^{144}R$ substitution, does not

reasonably provide enablement for any variant of any RP-II protease comprising modifications at one or more positions corresponding to 1, 2, 3, 4, 5, 6, 7, 8, 143, 144, 145, 146, 158, 159, 160, 161, 162, 194, 199, and 201 of SEQ ID NO: 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In regards to this enablement rejection, the application disclosure and claims are compared per the factors indicated in the decision In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). These factors are considered when determining whether there is sufficient evidence to support a description that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. The factors include but are not limited to: (1) the nature of the invention; (2) the breath of the claims; (3) the predictability or unpredictability of the art; (4) the amount of direction or guidance presented; (5) the presence or absence of working examples; (6) the quantity of experimentation necessary; (7) the relative skill of those skilled in the art. Each factor is here addressed on the basis of a comparison of the disclosure, the claims, and the state of the prior art in the assessment of undue experimentation.

Claims 47 and 76 are so broad as to encompass any variant of any RP-II protease comprising modifications at one or more positions corresponding to 1, 2, 3, 4, 5, 6, 7, 8, 143, 144, 145, 146, 158, 159, 160, 161, 162, 194, 199, and 201 of SEQ ID NO: 2. Claims 59 and 60 are so broad as to encompass any variant of any RP-II protease comprising modifications at positions corresponding to 144 or 144 and 161 of SEQ ID NO: 2. The scope of these claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides broadly encompassed by the claim. Since the amino acid sequence

of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. However, in this case the disclosure is limited to SEQ ID NO: 2 having a $H^{144}R$ substitution.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims. Furthermore, the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the results of such modifications are unpredictable (Galye et al, 1993; Whisstock et al, 2003). In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions. Moreover, the claim fails to recite any function for the encompassed variants and, thus, the skilled artisan is not enabled for testing for the desired activity or using the encompassed variants.

The specification does not support the broad scope of Claims 47 and 76, which encompasses all variants of all RP-II proteases comprising modifications at one or more positions corresponding to 1, 2, 3, 4, 5, 6, 7, 8, 143, 144, 145, 146, 158, 159, 160, 161, 162, 194, 199, and 201 of SEQ ID NO: 2. The specification does not support the broad scope of Claims 59 and 60, which encompasses all variants of all RP-II proteases comprising modifications at positions corresponding to 144 or 144 and 161 of SEQ ID NO: 2. The specification does not

support the broad scope of Claims 47, 59, 60, and 76 because the specification does not establish: (A) the structure of all proteins having RP-II glutamic-acid-specific endopeptidase activity; (B) regions of the protein structure which may be modified without affecting the glutamic-acid-specific endopeptidase activity; (C) the general tolerance of the glutamic-acid-specific endopeptidase activity to modification and extent of such tolerance; (D) a rational and predictable scheme for modifying any residues with an expectation of obtaining the desired biological function; and (E) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any variant of any RP-II protease comprising modifications at one or more positions corresponding to 1, 2, 3, 4, 5, 6, 7, 8, 143, 144, 145, 146, 158, 159, 160, 161, 162, 194, 199, and 201 of SEQ ID NO: 2. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the identity of sequences having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In support of their request that the analogous prior rejection be withdrawn, Applicants provide the following arguments, which are relevant here. The specification provides an extensive disclosure for producing the claimed polypeptide. The methods of making the claimed polypeptides and screening for RP-II protease activity are known in the art and described in the

specification. The specification discloses a number of parent RP-II proteases (SEQ ID NOs: 2, 4, 6, 8, 10, 12 and 14) and numerous variants within the scope of the claims. Given the extensive guidance given in the specification and the high level of skill in the art, the experimentation involved to produce other variants within the scope of the claims is routine and well within the skill of those in the art. A considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experiment should proceed."

These arguments are not found to be persuasive for the following reasons. It is acknowledged that a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance. It is also acknowledged that methods for making modified proteins and assays for glutamic-acid-specific endopeptidase activity were known in the art. However, the instant claims encompass any protein having any structure and having glutamic-acid-specific endopeptidase activity. The making and testing of all said proteins possibly having the desired activity clearly represents undue experimentation.

Written Description

Claims 47, 59, 60, and 76 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. These claims are directed to a genus of any variant of any RP-II protease comprising modifications at one or more positions corresponding to 1, 2, 3, 4, 5, 6, 7, 8, 143, 144, 145, 146, 158, 159, 160, 161, 162, 194, 199, and 201 of SEQ ID NO: 2. The

specification teaches the structure of only a few representative species of said variant protein molecules and all are derived from a single parent protease. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than being a variant of any RP-II protease comprising modifications at one or more positions corresponding to 1, 2, 3, 4, 5, 6, 7, 8, 143, 144, 145, 146, 158, 159, 160, 161, 162, 194, 199, and 201 of SEQ ID NO: 2. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

In support of their request that the analogous prior rejection be withdrawn, Applicants provide the following arguments, which are relevant here. The specification describes a number of other positions, including specific mutations, which can be combined with any of the claimed modifications. Thus, the specification fully describes the RP-II protease variants of the present invention.

These arguments are not found to be persuasive for the following reasons. It is acknowledged that specification describes a number of positions that can be modified. However, the instant claims encompass any protein having any structure and having glutamic-acid-specific endopeptidase activity. Description of said positions that can be modified fails to describe the full scope of any protein having any structure and having glutamic-acid-specific endopeptidase activity in a manner such that the skilled artisan would recognize that Applicants were in possession of the full scope of invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 47 and 76 are rejected under 35 U.S.C. 102(b) as being anticipated by Norregaard-Madsen et al, 2001 (IDS). Norregaard-Madsen et al teach variants of RP-II proteases, including BCL, wherein the variants have at least 60% homology to the parent sequence or are encoded by a polynucleotide that hybridizes to the parent polynucleotide under very low stringency conditions (pg 17, parg 2 to pg 19, parg 1). The skilled artisan would believe that, more likely than not, said variants of Norregaard-Madsen et al encompass variants of any RP-II protease comprising modification(s) at one or more positions corresponding to 1, 2, 3, 4, 5, 6, 7, 8, 143, 144, 145, 146, 158, 159, 160, 161, 162, 194, 199, and 201 of SEQ ID NO: 2. Norregaard-Madsen et al further teach detergent compositions comprising their variants. Therefore, Claims 47 and 76 are rejected under 35 U.S.C. 102(b) as being anticipated by Norregaard-Madsen et al, 2001.

Claims 47 and 59 are rejected under 35 U.S.C. 102(b) as being anticipated by Sloma et al, 1990. Sloma et al teach a protease having an Asp substitution at the position corresponding to

His^{144} of SEQ ID NO: 2. Therefore, Claims 47 and 59 are rejected under 35 U.S.C. 102(b) as being anticipated by Sloma et al, 1990.

Claims 47 and 59 are rejected under 35 U.S.C. 102(a&e) as being anticipated by Ostergaard et al, 2003 (filing date 17-APR-2000). Ostergaard et al teach a protease having a Met substitution at the position corresponding to His^{144} of SEQ ID NO: 2. Therefore, Claims 47 and 59 are rejected under 35 U.S.C. 102(a&e) as being anticipated by Ostergaard et al, 2003.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 76 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sloma et al, 1990 or Ostergaard et al, 2003 in view of Norregaard-Madsen et al, 2001. The teachings of Sloma et al and Ostergaard et al are described above. Sloma et al and Ostergaard et al do not teach detergent compositions comprising their variants. However, detergent compositions comprising proteases were well-known in the art (Norregaard-Madsen et al). It would have been obvious to a person of ordinary skill in the art to prepare detergent compositions comprising the variants Sloma et al and Ostergaard et al because said compositions can be used for cleaning. The expectation of success is high, as detergent compositions comprising proteases were well-known in the art. Therefore, Claim 76 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sloma et al, 1990 or Ostergaard et al, 2003 in view of Norregaard-Madsen et al, 2001.

Allowable Subject Matter

No claims are allowable.

Applicant's amendment necessitated any new grounds of rejection presented in this Office action. Any new references were cited solely to support rejection(s) based on amendment or rebut Applicants' arguments. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Regarding filing an Appeal, Applicants are referred to the Official Gazette Notice published July 12, 2005 describing the Pre-Appeal Brief Review Program.

Final Comments

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants' remarks, requests for extension of time, and any other distinct papers be submitted on separate pages. It is also requested that the serial number of the application and date of amendment be referenced on every page of the response.

It is also requested that Applicants identify support, within the original application, for any amendments to the claims and specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Nashed can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published application may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on the access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SHERIDAN SWOPE/
Primary Examiner, Art Unit 1652